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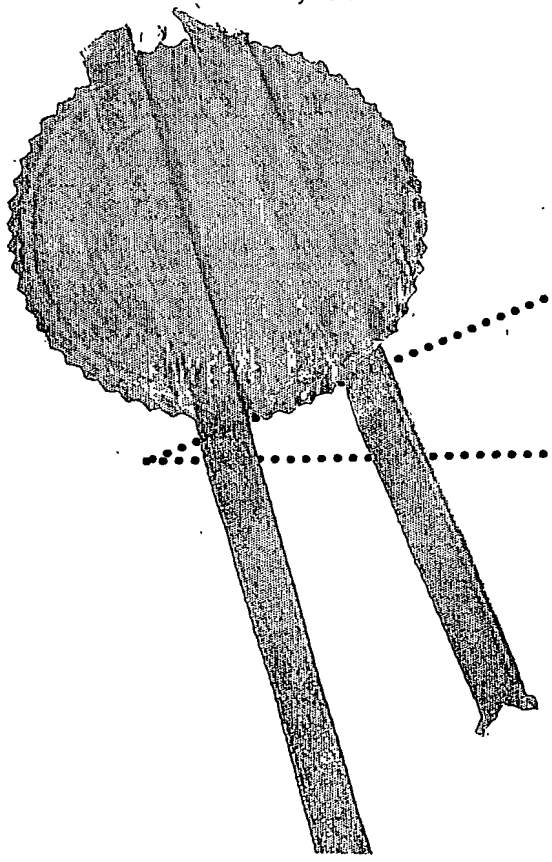
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 14/02/2003 in respect of Patent Application No.193/MUM/2003 of M/S. CIPLA LIMITED, 8, Bellasis Road, Mumbai Central, Mumbai-400 008, Maharashtra, India, An Indian Company incorporated under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.



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Dated this 22nd day of June 2004.

(R. BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS.

ORIGINAL

14 FEB 2003

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See section 7]

1. We,

   (a) M/S. CIPLA LIMITED

   (b) 8, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India

   (c) Indian company incorporated under the Companies Act 1956

2. Hereby declare –

   (a) that we are in possession of an invention titled "**IMPROVED PROCESS FOR PREPARATION OF PROTON PUMP INHIBITORS**"

   (b) that the Provisional Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

   (a) Kankan, R.N.
   (b) A-3/5, N.B.D. Society
   N.S.S.Road, Ghatkopar
   Mumbai 400 084
   Maharashtra, India
   (c) Indian National

   (a) Rao, D.R.
   (b) 4/403, Garden Enclave,
   Pokhran Road 2
   Thane(W) 400 601
   Maharashtra, India
   (c) Indian National

193/mum/2003

193 | 14/2/2003 मुंबई MUM 2003

14 FEB 2003

Received Rs. 5000 in Cash 14/2/03
Vide Entry No. 2391 in the Register of Valuables, Bombay.
14-02-03

(a) **Pathi, S.L.**
(b) 2475/24, 7th B Main
R P C Layout, Vijaynagar
Bangalore 560 040
Karnataka, India
(c) Indian National

(a) **Narayan, B.M.**
(b) 103/Sarita Co-Op Hsg Society
I.C. Colony, Borivili (W)
Mumbai 400 103
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

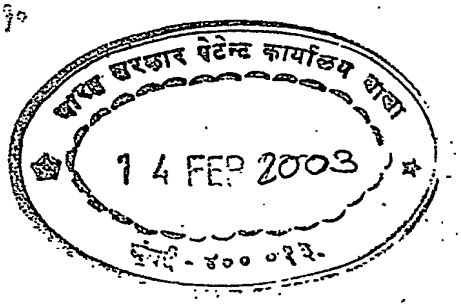
6. **Following declaration was given by the inventor(s) :**

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Kankan, Rajendra Narayanrao)

(Rao, Dharmaraj Ramachandra)

(Pathi, Srinivas Laxminarayan)



(Narayan, Bhanu Manjunath)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:
   (a) Provisional specification (3 copies)
   (b) Statement and Undertaking on Form 3
   (c) Form 26
   (d) Fee Rs.5000/- in cheque bearing No.625588 dated 13th February 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 13th day of February 2003

DR. GOPAKUMAR G. NAIR
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road
Kandivli (East), Mumbai – 400 101

To

The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION

[See section 10]

"IMPROVED PROCESS FOR PREPARATION OF PROTON PUMP INHIBITORS"

(a) **CIPLA LTD.**

(b) **8, Bellasis Road, Mumbai Central, Mumbai – 400 008, Maharashtra, India**

(c) Indian Company incorporated under the Companies Act 1956

ORIGINAL

The following specification describes the nature of the invention and the manner in which it is to be performed:

IMPROVED PROCESS FOR PREPARATION OF PROTON PUMP INHIBITORS

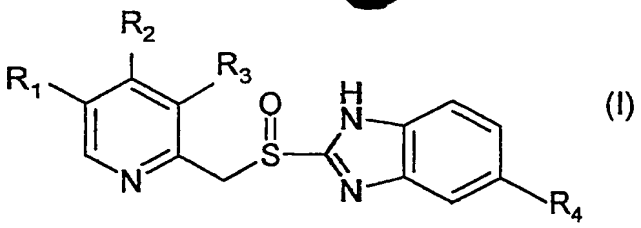
[0001] Field of the Invention

[0002] This invention in general relates to an improved process for preparation of proton pump inhibitors, more particularly to a simple and cost effective, eco-friendly and green chemistry process for oxidation of sulphides.

[0003] Background of the Invention

[0004] Gastric Proton Pump Inhibitors (PPIs) are compounds having several substituted 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles such as Lansoprazole (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]sulfinyl]1H-benzimidazole, Omeprazole ((5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyirdyl)methyl]sulfinyl]-1H-benzimidazole, Pantoprazole ((5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]1H-benzimidazole and Rabeprazole (2-[[[4-(3-methoxy-propoxy)3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole. These compounds produce profound and sustained inhibition of gastric acid secretion. Responses of PPIs are more rapid than with other anti-secretory drugs. The PPIs work by completely blocking the production of stomach acid. They do this by inhibiting or shutting down a system in the stomach known as proton pump, the full name of which is "hydrogen-potassium adenosine triphosphate enzyme system". PPIs are the drug of choice in dyspepsia and peptic ulcers. In the treatment of peptic ulcers, the RRs of PPIs are superior to other drugs. PPIs are also drugs of choice in Zollinger-Ellyson syndrome.

[0005] The reported synthesis of these substituted 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles principally involves generally an oxidation process of a sulfide compound to a sulfinyl compound of formula I.



(I)

[0006] Prior art processes addressed at the preparation of 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles involve the synthesis of the corresponding thioether compound, and its subsequent oxidation to the sulfinyl or sulfoxy compound, by various methods such as reaction with hydrogen peroxide over a vanadium compound catalyst and reaction with peracids, peresters, ozone. There are several disadvantages associated with the known processes, primarily with respect to the nature of the thioether (or sulfide) compound being oxidized.

[0007] U. S. Patent No. 4,628,098 to Nohara, et al. discloses a process for preparation of Lansoprazole by oxidation of its sulphides using peracids (m-chloro perbenzoic acid). The object of this invention was to prepare an anti-ulcer agent having actions of inhibiting gastric acid secretion, of protecting gastric mucosa and of antagonizing ulceration.

[0008] U. S. Patent No. 5,840,552 to Holt, et al. discloses a process for preparation of Lansoprazole wherein sulphides are selectively bio-oxidised to isolate the pharmaceutically active enantiomer or enantiomerically enriched sulfoxide form, using microorganisms or microbial enzyme system.

[0009] U. S. Patent No. 5,374,730, to Slemon, et al discloses a process for the preparation of Omeprazole and Lansoprazole wherein amide analogues of the thioether compounds are readily oxidized to the corresponding sulfinyl compounds and the sulfinyl compounds are hydrolyzed in alkaline medium to the corresponding carboxylic acid salts which can be decarboxylated to Omeprazole or Lansoprazole, as the case may be. The disclosure refers to the advantages in relation to the purity in which the final products

can be obtained, and the simplicity of the purification procedures. The amide compounds which are subjected to the oxidation step are crystalline solids, as opposed to oils, so that they are readily purified to a high degree of purity by relatively simply precipitation, crystallization and washing procedures. The carboxylates and carboxylic acid salts which are formed in the next synthetic step after oxidation are water soluble, whereas the final products, Omeprazole and Lansoprazole, are not. Accordingly, any un-reacted residues of these compounds and many other minor impurities in the final products are simply removable by an aqueous washing procedure. Avoidance of significant discoloration of the product is the other advantage disclosed.

[0010] United States Patent No. 5,470,983 to Slemon, et al. titled 'Preparation of Omeprazole and ansoprazole, and intermediates useful therein' discloses processes for producing Lansoprazole from acetamide-sulfide compounds by a process of oxidation to form the amide sulfinyl compound, followed by alkaline hydrolysis to the sulfinyl carboxylate or salt, and decarboxylation.

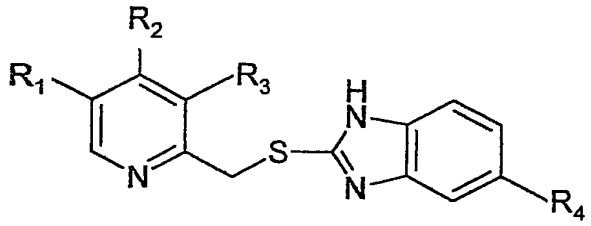
[0011] United States Patent No. 5,502,195, to Slemon, et al. is a Continuation-in-Part of application Ser. No. 276,378, which is in turn a division U.S. Pat. No. 5,374,730. This disclosure is addressed at a process for preparation of Lansoprazole, which is identical to the processes recited in issues Patent No.5, 470,983, wherein the acetamide sulphide is oxidized to amide sulfinyl compounds, which is then hydrolysed in alkaline medium to the carboxylic acid salts and then decarboxylated to form Lansoprazole.

[0012] United States Patent No. 6,423,864 to Moon, et al. refers to the oxidation procedures employed in the prior art methods for converting a compound into Lansoprazole as having problems in that many byproducts are formed and the yield of Lansoprazole is low. EP Patent No. 134,400, GB Patent No. 2,134,523, U.S. Pat. No. 4,628,098, Korean Patent No. 52,837 discloses m-chloroperbenzoic acid as the oxidant. Spanish Patent Nos. 550,057, 540,147 and 539,793 disclose sodium periodate, iodosomethylbenzene and iodosobenzene, respectively, as the oxidant employed. These prior art processes have been cited to be unviable because of the expensive oxidants used therein which is also resulting in the

production of many impurities and a low yield of the product in the range of about 60 to 80%.

[0013] All these prior art process either use expensive catalysts or hazardous oxidizing reagents such as peracids which are not suitable for commercial manufacture of these compounds. Also over-oxidation of the thioether compound to the corresponding sulphone analogue is a common problem encountered with prior art processes.

[0014] There has been a long felt need for efficient and safe methods for the selective oxidation of a sulphide compound of the formula II

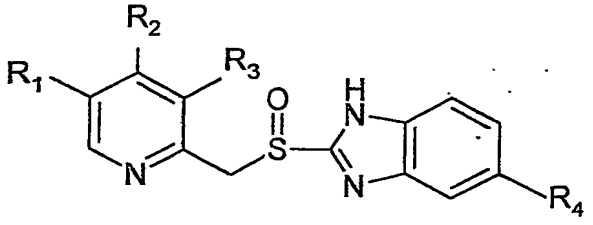


(II)

to a sulfinyl compound of the formula I. The present invention provides an efficient, safe and industrially feasible method for preparing various substituted 2-(2-pyridylmethyl)-sulfinyl-1H-benzimidazoles.

[0015] SUMMARY OF THE INVENTION:

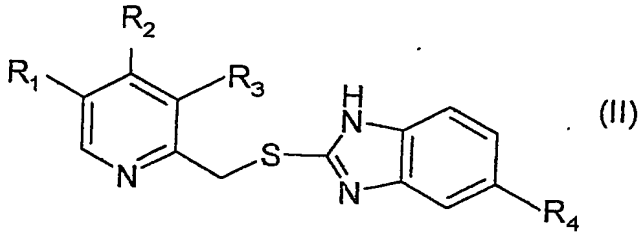
[0016] The present invention provides a process for preparing a sulfinyl compound of the formula I



(I)

[0017] Wherein R_1 and R_3 are selected from hydrogen, methyl or lower alkoxy , R_2 are selected from substituted or unsubstitued lower alkoxy and R_4 are selected from hydrogen or substituted or unsubstitued lower alkoxy,

[0018] Comprising oxidation of a sulfide compound of the formula II



(II)

[0019] Wherein R_1, R_2, R_3 and R_4 have the same meaning as mentioned above to produce by selective oxidation compound of the formula I

[0020] The present invention further provides a process for preparing a sulfinyl compound of the formula I, comprising reacting a sulfide compound of the formula II with aqueous hypochlorite solution.

[0021] The present invention further provides a process for preparing a sulfinyl compound of the formula I, comprising reacting a sulfide compound of the formula II with aqueous hypochlorite solution optionally in the presence of a catalyst selected from pyridine, diisopropyl ethyl amine, N,N-dimethyl amino pyridine.

[0022] The object of the present invention is to provide an improved process for selective oxidation of (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]thio]1H-benzimidazole to the corresponding (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]-sulfinyl]1H-benzimidazole (Lansoprazole), using an eco-friendly, inexpensive and readily available reagent

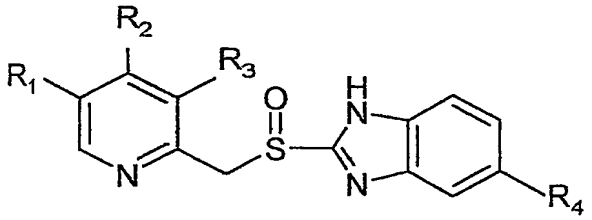
[0023] Another object of the present invention is to provide an improved process for selective oxidation of ((5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyirdyl)methyl]-thio]-1H-benzimidazole, to the corresponding ((5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyirdyl)methyl]-sulfinyl]-1H-benzimidazole (Omeprazole), using an eco-friendly, inexpensive and readily available reagent.

[0024] Another object of the present invention is to provide an improved process for selective oxidation of ((5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]1H-benzimidazole, to the corresponding ((5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl]1H-benzimidazole (Pantoprazole), using an eco-friendly, inexpensive and readily available reagent.

[0025] Another object of the present invention is to provide an improved process for selective oxidation of (2-[[[4-(3-methoxy-propoxy)3-methyl-2-pyridinyl]methyl]-thio]-1H-benzimidazole, to the corresponding (2-[[[4-(3-methoxy-propoxy)3-methyl-2-pyridinyl]methyl]-sulfinyl]-1H-benzimidazole (Rabeprazole), using an eco-friendly, inexpensive and readily available reagent.

[0026] **DETAILED DESCRIPTION OF THE INVENTION**

[0027] The present invention provides a process for preparing a sulfinyl compound of

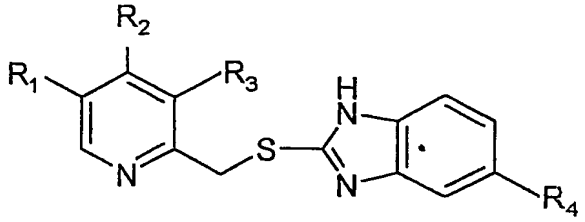


(I)

the formula I

[0028] Wherein R_1 and R_3 are selected from hydrogen, methyl or lower alkoxy, R_2 are selected from substituted or unsubstituted lower alkoxy and R_4 are selected from hydrogen or substituted or unsubstituted lower alkoxy,

Comprising oxidation of a sulfide compound of the formula II



(II)

[0029] Wherein R_1, R_2, R_3 and R_4 have the same meaning as mentioned above to produce by selective oxidation compound of the formula I

[0030] In one embodiment, the present invention discloses a process for producing sulfinyl compounds. The process comprises dissolving or suspending the sulphide precursor in suitable solvents or mixture of solvents. Sodium hypochlorite is added slowly in a controlled manner at appropriate temperature conditions to give after simple work up procedures the sulfinyl compounds in very high yield and purity.

[0031] The present invention discloses a process for producing sulfinyl compounds comprising adding the corresponding sulphide to solvent, which solvent comprises water, lower alkyl alcohols, esters or ethers and chlorinated solvents or mixtures thereof. The preferred solvents are water, methanol, ethanol, isopropanol, di-isopropyl ether, dichloromethane, acetonitrile, ethyl acetate or mixture of two or more of these.

[0032] The process of the present invention can be performed at temperatures varying from –30 to 50°C. However, the preferred temperatures are between 0°C to 30°C. Sodium hypochlorite as an aqueous solution can be of varying strengths ranging from 2% to 30%, though we prefer to use a concentration in the range of 2% to 5% for ease of handling.

[0033] It is understood that the process of the present invention can be performed using other related oxidizing agents such as sodium hypobromite or calcium hypochlorite.

[0034] The process of the present invention can be performed optionally in the presence of suitable catalyst such as pyridine, di-isopropyl ethyl amine, N,N-dimethyl amino pyridine to avoid formation of undesirable byproducts.

[0035] One can use commercially available sodium hypochlorite solutions, but it is advantageous to use a freshly prepared solution having about 0.5% to 5% of free sodium hydroxide. The presence of free sodium hydroxide not only stabilizes the hypochlorite but also has a positive impact on the reaction, since the products are known to be unstable to acidic conditions.

[0036] Alternatively, a solution of sodium hydroxide or any other alkali can be added to the suspension or solution of the sulphide in the solvent or mixture of solvents before addition of the oxidizing solution.

[0037] The time taken for addition of the hypochlorite solution can range from several minutes to several hours depending on the strength of the solution and the exothermicity of the reaction. We prefer to perform the addition slowly over a period ranging from 30 minutes to 4 hours. The time taken for completion of the reaction can range from 2 hours to 10 hours.

[0038] The product is isolated from the reaction mass by adjusting the pH using aqueous organic or inorganic acids. Normally, the pH is adjusted between 6.0 to 9.5 more preferably between 7 to 7.5 using aqueous acetic acid, followed by filtration to isolate the product.

[0039] In another embodiment, the process comprises of purifying the resultant of process herein above described by dissolving it in mixture of methanol and aqueous sodium hydroxide solution. The pH of the clear solution is adjusted between 9.0 to 9.5 using aqueous ammonium acetate solution and product isolated by filtration.

[0040] The preferred compound prepared according to the process of the present invention is Lansoprazole.

[0041] The preferred compound prepared according to the process of the present invention is Omeprazole.

[0042] The preferred compound prepared according to the process of the present invention is Pantoprazole.

[0043] The preferred compound prepared according to the process of the present invention is Rabeprazole

[0044] The process of the present invention is illustrated by the following examples and in no way limits the scope of this invention. While the present invention is described above in connection with preferred or illustrative embodiments, these embodiments are not intended to be exhaustive or limiting of the invention. Rather, the invention is intended to cover all alternatives, modifications and equivalents included within its spirit and scope, as defined by the appended claims

[0045] **Example 1**

[0046] Perparation of 2-[[[4-(3-methoxy-propoxy)-3-methyl-2-pyridinyl] methyl]-sulfinyl]-1H-benzimidazole (Rabeprazole).
2-[[[4-(3-methoxy-propoxy)-3-methyl-2-pyridinyl]methyl]-thio]-1H-benzimidazole (10 grams) is suspended in 200 ml of Purified Water and pyridine (4 ml). To this is slowly added 75 grams of 3.8% Sodium hypochlorite solution in 2 hours. The reaction mass is maintained at 5 - 8° C for 4 hours.. After reaction completion, the excess Sodium hypochlorite is decomposed using 5% aqueous Sodium thiosulphate solution. The pH is adjusted between 8.0 to 9.0 using 10% Ammonium acetate solution. Acetone is added and the reaction mixture stirred for 20 hours at 10°C. The product is filtered and washed with water and dried in an oven.

[0047] **Example 2**

[0048] Preparation of 5-(difluoromethoxy)-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole (Pantoprazole)

[0049] 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]-thio]-1H-benzimidazole (10 grams) is dissolved in purified water (100 ml) and Methanol (10 ml). 80 grams of 3.5% aqueous Sodium hypochlorite solution is added to the reaction mass maintaining 5 - 8° C in about 1 hour. Excess Hypochlorite is decomposed using 5% aqueous Sodium thiosulphate solution. pH of the reaction mass is adjusted to 8.0 – 9.5 using Ammonium acetate. The solids are filtered, washed with chilled water and dried in an oven to give 8.5 g of the title compound.

[0050] **Example 3**

[0051] Preparation of (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]-sulfinyl]1H-benzimidazole (Lansoprazole)

[0052] (2-[[[3-methyl-4-(2,2,2-trifluoro-ethoxy)-2-pyridinyl]methyl]-thio]1H-benzimidazole (10 grams) is suspended in 100 ml of a mixture of acetonitrile and water (7:3). 61 grams of Sodium hypochlorite solution (4.2%) is added over a period of 4 hours maintaining a temperature of 5°C – 10°C. Excess Hypochlorite is decomposed using 3% aqueous Sodium metabisulfite solution. Acetone (50 ml) is added and the pH is adjusted between 7.5 to 8.5 using dilute acetic acid. The solids are filtered, washed with chilled water and dried in an oven to give 8 g of the title compound.

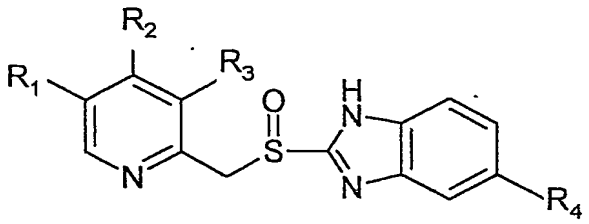
[0053] **Example 4**

[0054] Preparation of ((5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyirdyl)methyl]sulfinyl]-1H-benzimidazole, (Omeprazole)

[0055] ((5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyirdyl)methyl]-thio]-1H-benzimidazole, (20 grams) is suspended in 200 ml of Dichloromethane. 140 grams of Sodium hypochlorite solution (4.2%) is added over a period of 3 hours maintaining a temperature of -5°C to 0°C. The organic layer is separated and extracted with 200 ml of 5% sodium hydroxide solution. The pH of the aqueous layer is adjusted to between 8-8.5 using dilute acetic acid. The solids are filtered, washed with chilled water and dried in an oven to give 17g of the title compound.

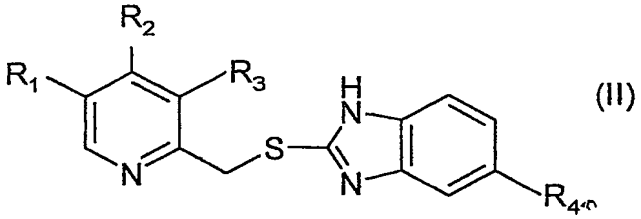
We claim:

1. A process for preparing a pyridine benzimidazole sulfinyl compound of formula I



(I)

Wherein R_1, R_2,and R_4 are each selected from the group consisting of hydrogen, substituted or unsubstituted lower alkyl and substituted or un-substituted lower alkoxy and R_3 is selected from the group consisting of hydrogen and substituted or un-substituted lower alkyl, comprising reacting a sulfide compound for formula II



(II)

wherein R_1 through R_4 are as in formula I, with an oxidizing agent to produce a sulfinyl compound of formula I after selective oxidation of sulphide compound of formula II.

2. A process according to claim 1 where the sulfinyl compound is a proton pump inhibitor.
3. A process according to claim 1 wherein the oxidizing agent is a aqueous hypochlorite or a hypobromite solution.

4. A process according to claim 3 wherein the oxidizing agent is aqueous sodium hypochlorite solution
5. A process according to claim 4 where in the concentration of the sodium hypochlorite solution is between 2% to 5 %.
6. A process according to claim 3 and 4 wherein the sodium hypochlorite solution contains 0.5% to 5% of free sodium hydroxide.
7. A process according to claim 1 wherein the oxidation is performed at a temperature ranging from –30 to 50°C.
8. A process according to claim 1 wherein the oxidation is performed in a solvent or solvent mixtures selected from water, methanol, isopropanol, acetonitrile, dichloromethane, and ethyl acetate.
9. A process for producing a proton pump inhibitor, the process comprising:
   adding a pyridine-benzimidazole sulfide compound to a solvent to form a mixture;
   cooling down the mixture to a controlled temperature;
   adding a hypochlorite solution to the mixture, in a controlled manner;
   maintaining the reaction at the controlled temperature for a pre-determined period;
   adjusting the pH range;
   isolating the resultant precipitate to produce the proton pump inhibitor.
10. A process according to claim 9, wherein the reaction is performed optionally in presence of bases selected from pyridine, diisopropyl ethyl amine, N,N-Dimethyl amino pyridine.
11. A process according to claim 9, wherein the addition of the hypochlorite solution is reaction is preceded by addition of an alkali solution.
12. A process according to claim 9 wherein the pH is adjusted in the range between 7.5 to 9.5 using dilute aqueous acid solutions.
13. A process for producing a proton pump inhibitor, the process comprising:
    adding a pyridine-benzimidazole sulfide compound to a solvent to form a mixture;
    adjusting the pH of the mixture between 9 to 12 using alkali metal hydroxide solution
    adding an organic base;

cooling down the mixture to a controlled temperature;

adding an oxidizing agent to the mixture in a controlled manner;

maintaining the reaction at the controlled temperature for a pre-determined period;

adjusting the pH range;

isolating the resultant precipitate to produce the proton pump inhibitor.

14. A process according to any of the preceding claims wherein the pyridine benzimidazole sulfinyl compound is Omeprazole.
15. A process according to any of the preceding claims wherein the pyridine benzimidazole sulfinyl compound is Lansoprazole
16. A process according to any of the preceding claims wherein the pyridine benzimidazole sulfinyl compound is Pantoprazole
17. A process according to any of the preceding claims wherein the pyridine benzimidazole sulfinyl compound is Rabeprazole.
18. A process according to any of the preceding claims where in the pyridine benzimidazole sulfinyl compound is converted optionally to its pharmaceutically acceptable salts, hydrates and solvates thereof.
19. A pharmaceutical composition containing a pyridine benzimidazole sulfinyl compound or its salt prepared according to any of the above claims.

Dated this the 13th day of February 2003

DR. GOPAKUMAR G. NAIR
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road
Kandivli (East), Mumbai – 400 101

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